PATENT SPECIFICATION 966,562

NO DRAWINGS.

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Date of Application and filing Complete Specification :
April 6, 1961. *No. 12477/61.*

966,562

Complete Specification Published : Aug. 12, 1964.

Index at Acceptance :—C2 C(1Q2, 1Q3, 1Q4, 1Q6C, 1Q8A, 1Q9B, 1Q9C, 1Q9F2, 1Q9G, 1Q9L, 1Q11G, 1Q11J.

International Classification :—A 61 k, C 07 d.

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COMPLETE SPECIFICATION.

Amine Compounds and Means of Producing the Same.

We, PARKE, DAVIS & COMPANY, a Corporation organized under the laws of the State of Michigan, one of the United States of America, of Joseph Campau at the River, Detroit, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement :

This invention relates to 5-fluoro-α-methyltryptamine, acid addition salts thereof and to processes for production of the same.

The free base product of the invention, 5-fluoro-α-methyltryptamine, forms addition salts with organic and inorganic acids. Such salts are preferred for those cases where water solubility is a desired property. Among the many organic and inorganic acid addition salts contemplated by the invention are the hydrochloric, hydrobromic, *p*-toluenesulfonic, sulfamic, sulfuric, phosphoric, acetic, citric and tartaric acid addition salts. The products of the invention possess a stimulant action on the central nervous system of living mammals and are therefore useful as analeptic agents, e.g. as psychic energizers for combatting depressive states, or as anorectic agents for alleviation of obesity in living mammals. Additionally, the products, both final and intermediate products, are also useful as starting materials for the production of other products having similar and other uses.

In accordance with one embodiment, the process of the invention is characterized in that 5-fluoro-3-(2-methyl-2-nitrovinyl)indole is subjected to reduction by reaction in the presence of an anhydrous non-hydroxylic organic solvent with lithium aluminium hydride or with a complex oxidizible metal borohydride such as sodium, potassium or lithium borohydride, in the presence of aluminium chloride and by decomposition of the resulting reaction complex with water or an aqueous medium. The reaction proceeds without application of external heating and, following addition of the reducing agent, it is preferred to maintain the reaction mixture at elevated temperature, more preferably at the reflux temperature of the reaction mixture, to accomplish prompt completion of the reaction. As solvents for the reaction, anhydrous non-hydroxylic organic solvents such as dioxan, diethyleneglycol dimethyether and tetrahydrofuran are employed. After completion of the reaction, the reaction product is subjected to decomposition by treatment with water or other aqueous medium. Decomposition is ordinarily carried out at room temperature ; and since the reaction is exothermic, external cooling may be applied.

According to another embodiment, the process of the invention is characterized in that 5-fluoro-3-(β-nitro-α-propenyl)indole is subjected to treatment with iron and acetic acid in the presence of water and an inert water-miscible organic solvent, and the resulting 3-(5-fluoro)-indolyl acetone is subjected to reductive amination by means of catalytic hydrogenation in the presence of aqueous ammonia. For the preparation of the indolyl acetone, at least two equivalents and preferably an excess of iron, as a powder, are employed for each equivalent of 5-fluoro-3-(β-nitro-α-propenyl)indole. Acetic acid of sufficient strength and concentration in the reaction mixture is employed to maintain the latter strongly acidic throughout the reaction, and inert water-miscible organic solvents such

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as ethanol, isopropanol, dioxan or tetrahydrofuran are employed. The reaction temperature can be varied considerably, preferably in the range from about 50 to 100° C. and for best results at the reflux temperature of the reaction mixture. The reaction is carried out under conditions such that excess 5-fluoro-3-(β-nitro-α-propenyl)indole in the reducing mixture is kept to a minimum. Preferably for this purpose, the reaction is carried out with a reflux apparatus of the Soxhlet type in which the indole starting material is placed in the Soxhlet thimble located in a side arm below the condenser so that the starting material is slowly leached into the reaction flask by condensate and vapor, refluxing being continued at least until the indole compound is completely taken up in the reaction mixture. The reductive amination step is carried out by means which *per se* are conventional, using hydrogen gas and ammonia under elevated pressure and temperature in the presence of a metal hydrogenation catalyst such as Raney nickel. The pressure and temperature for the reaction are subject to wide variation. In general, hydrogen pressures of at least about 50 atmospheres, preferably 75 to 100 atmospheres, and temperatures from about 50 to 100° C. or higher, preferably 60 to 75° C., are employed. The reaction is favored by the use of an inert water-miscible solvent such as ethanol, *n*-propanol, isopropanol, dioxan or tetrahydrofuran.

In accordance with a still further embodiment, the process of the invention is characterized in that 5-fluoro-3-hydroxy-3-2¹-oximinopropyl-oxindole is subjected to reduction by reaction in the presence of an anhydrous non-hydroxylic organic solvent with lithium aluminium hydride or with a complex oxidizible metal borohydride in the presence of aluminium chloride and by decomposition of the resulting reaction complex with water or an aqueous medium. The starting material is prepared by reaction of hydroxylamine with 3-acetonyl-3-hydroxy-5-fluoro-oxindole, which reaction may be carried out over a wide range of temperature, conveniently from room temperature to about 150° C. and preferably at the reflux temperature of the reaction mixture. The hydroxylamine is preferably supplied in the form of an acid addition salt such as the hydrochloride salt, and the reaction mixture is maintained at neutrality by addition of a basic agent such as sodium hydroxide, sodium acetate or pyridine. To facilitate the reaction in which the hydroxylamine is supplied in water-soluble salt form, the reaction is carried out in an inert water-miscible solvent such as ethanol or isopropanol. For the reduction step one may employ lithium aluminium hydride or, alternatively, a complex oxidizible metal borohydride (e.g. sodium, potassium or lithium borohydride) in the presence of aluminium chloride as indicated. The reaction proceeds without application of external heat and, following addition of the reducing agent, it is preferred to maintain the reaction mixture at elevated temperature, more preferably at the reflux temperature of the reaction mixture, to accomplish prompt completion of the reaction. As solvents for the reaction, anhydrous non-hydroxylic organic solvents such as dioxan, diethyleneglycol dimethyl ether and tetrahydrofuran are employed. After completion of the reaction, the reaction product is subjected to decomposition by treatment with water or other aqueous medium. Decomposition is ordinarily carried out at room temperature and since the reaction is exothermic, external cooling may be applied.

The products of the process can be isolated in free base form or in the form of the acid addition salt. Thus, where an acid is present in the reaction mixture, the product is obtained in addition salt form with the acid and can be converted to the free base by neutralization with a basic agent. Other acid addition salts can be obtained by reaction of the free base with any desired acid, either organic or inorganic, and isolation thereof is facilitated by formation of the salt of the acid in a medium in which the salt is insoluble, thereby permitting recovery of the salt as an insoluble precipitate.

The invention is illustrated by the following examples :—

EXAMPLE 1.

A solution of 5-fluoroindole (9.7 g. ; J. Chem Soc., 1955, 1283) in 10 ml. of dimethylformamide is added to a stirred solution of phosphorous oxychloride (8.2 ml.) in dimethylformamide (25 ml.) at 20—30° C. After the addition is complete, the mixture is stirred at 35—40° C. for 45 minutes, cooled and then treated with crushed ice (200 g.). A solution of sodium hydroxide (16 g.) in water (80 ml.) is added to the mixture at a rate such that the mixture remains acid during addition of three-fourths of the solution ; the last portion of the solution is added rapidly and the resulting mixture is boiled for one minute. The product, 5-fluoro-3-indolealdehyde, separates in crystalline form upon cooling of the reaction mixture ; m.p. 160—162° C.

5-Fluoro-3-indolealdehyde (9.2 g.) is added to nitroethane (35 ml.) containing ammonium acetate (1.7 g.) and the mixture is refluxed for one-half hour. The product, 5-fluoro-3-(2-methyl-2-nitrovinyl)indole, which separates on cooling is collected by filtration and recrystallized from ethanol ; m.p. 179—180° C. A mixture of the product (8.6 g.) in 100 ml. of dry tetrahydrofuran is added to a suspension of lithium aluminium hydride (10 g.) in

dry ether (50 ml.) and dry tetrahydrofuran (80 ml.). The mixture is heated at reflux for four hours, cooled, cautiously treated with water (10 ml.), refluxed for ten minutes and then filtered. The filtrate is evaporated, the residue dissolved in dry ether and the product precipitated by the addition of an ethereal solution of hydrogen chloride in excess. The product, 5-fluoro-α-methyltryptamine hydrochloride, is collected and recrystallized from methanol-ether (1 : 1); m.p. 225—226° C. (decomp.).

EXAMPLE 2.

A mixture of reduced iron powder (20 g.), water (50 ml.), alcohol (50 ml.) and glacial acetic acid (4 ml.) is placed in a flask fitted with a side arm condenser and a Soxhlet thimble containing 10.9 g. of 5-fluoro-3-(2¹-nitro-2¹-methylvinyl)indole. The mixture is stirred well and heated to reflux. Refluxing is continued until the leaching action of the condensed vapor accomplishes the transfer of the starting material in the thimble into the flask. The reaction mixture is then made alkaline by addition of dilute aqeuous sodium hydroxide solution and the alkaline mixture is filtered. The iron precipitate (filter cake) is washed by boiling and stirring with 95% alcohol and the combined filtrate and washings are concentrated to a small volume by evaporation *in vacuo*. 5-Fluoro-3-indolylacetone which separates on standing, is collected by filtration and crystallized from ether. The product, in the amount of 9.5 g., is mixed with concentrated ammonium hydroxide (10 ml.; density 0.88) and Raney nickel hydrogenation catalyst (2 g.) in an autoclave and the volume is adjusted to 50 ml. with ethanol. The mixture is heated to 75 to 85° C. under hydrogen pressure of about 100 atmospheres and the autoclave is then rotated for 24 hours whereupon it is cooled, vented and the catalyst removed by filtration. The filtrate is concentrated by evaporation *in vacuo* to remove the solvent, the residual crude free base product is taken up in ether and the resulting solution acidified by addition of excess hydrogen chloride in ether. The desired product in crystalline form, 5-fluoro-α-methyltryptamine hydrochloride, is recovered by filtration of the ethereal mixture; m.p. 225—226° C. (decomp.) after recrystallization from methanol-ether.

EXAMPLE 3.

3 - Acetonyl - 3 - hydroxy - 5 - fluoro-oxindole (9.5 g.) is dissolved in hot ethanol (50 ml., 96%) and hydroxylamine hydrochloride (3.5 g.; 0.05 mol.) in water (10 ml.) is added. The resulting solution is neutralized with 2N aqueous sodium hydroxide solution using bromophenol Blue external indicator. Removal of about 30 ml. of alcohol under reduced pressure, dilution with water and cooling cause separation of the product, 3 - acetonyl - 3 - hydroxy - 5 - fluoro - oxindoleoxime, which is collected and dried. The product (in the amount of 7.9 g.) in tetrahydrofuran (50 ml.) is added dropwise as a slurry to a stirred suspension of lithium aluminium hydride (10 g.) in tetrahydrofuran (50 ml.). On completion of the addition the mixture is heated under reflux for four hours. The reaction mixture after cooling is decomposed by the gradual addition of a minimum amount of water, the aqueous mixture is filtered, the filtrate dried and concentrated by evaporation under vacuum and the residual crude free base product, 5-fluoro-α-methyltryptamine, is taken up in ether. The ethereal solution is treated with an excess of saturated hydrogen chloride in ether and the product which precipitates, 5 - fluoro - α - methyltryptamine hydrochloride, is collected and recrystallized from methanol-ether; m.p. 225—226° C. (decomp.).

The starting material, 3-acetonyl-3-hydroxy-5-fluoro oxindole, is prepared from 5-fluoroisatin as follows: 5-fluoroisatin (13.2 g.) is suspended in acetone (150 ml.) and diethylamine (4 ml.) is added. The mixture is allowed to stand at room temperature first for three to four hours with occasional stirring and then overnight. The product which separates, 3 - acetonyl - 3 - hydroxyl - 5-fluoro oxindole, is collected by filtration and is washed with acetone and dried.

In order to prepare the citric acid salt, a solution of the free base in isopropanol is mixed with a solution of one equivalent of citric acid in isopropanol. Removal of the solvent under reduced pressure leaves the desired citric acid salt of 5-fluoro-α-methyltryptamine. Other acid addition salts such as the hydrobromide, sulfate, sulfamate and *p*-toluenesulfonate can be prepared in the same manner by substituting in this procedure one equivalent of the respective acids for citric acid.

WHAT WE CLAIM IS:—

1. 5-Fluoro-α-methyltryptamine and acid addition salts thereof.
2. 5-Fluoro-α-methyltryptamine.
3. 5 - Fluoro - α - methyltryptamine hydrochloride.
4. A method of producing 5-fluoro-α-methyltryptamine and acid addition salts thereof, substantially as described in any one of the foregoing examples.

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Abingdon: Printed for Her Majesty's Stationery Office, by Burgess & Son (Abingdon), Ltd.—1964.

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